The Royal College of Surgeons of England

UROLOGY

Ann R Coll Surg Engl 2009; **91**: 399–403
doi 10.1308/003588409X428289

Ultrasensitive prostate specific antigen assay following laparoscopic radical prostatectomy – an outcome measure for defining the learning curve

R VINEY, L GOMMERSALL, J ZEIF, D HAYNE, ZH SHAH, A DOHERTY

Department of Urology, Queen Elizabeth Hospital, Birmingham, UK

ABSTRACT

INTRODUCTION Radical retropubic prostatectomy (RRP) performed laparoscopically is a popular treatment with curative intent for organ-confined prostate cancer. After surgery, prostate specific antigen (PSA) levels drop to low levels which can be measured with ultrasensitive assays. This has been described in the literature for open RRP but not for laparoscopic RRP. This paper describes PSA changes in the first 300 consecutive patients undergoing non-robotic laparoscopic RRP by a single surgeon.

OBJECTIVES To use ultrasensitive PSA (uPSA) assays to measure a PSA nadir in patients having laparoscopic radical prostatectomy below levels recorded by standard assays. The aim was to use uPSA nadir at 3 months' post-prostatectomy as an early surrogate end-point of oncological outcome. In so doing, laparoscopic oncological outcomes could then be compared with published results from other open radical prostatectomy series with similar end-points. Furthermore, this end-point could be used in the assessment of the surgeon's learning curve.

PATIENTS AND METHODS Prospective, comprehensive, demographic, clinical, biochemical and operative data were collected from all patients undergoing non-robotic laparoscopic RRP. We present data from the first 300 consecutive patients undergoing laparoscopic RRP by a single surgeon. uPSA was measured every 3 months post surgery.

RESULTS Median follow-up was 29 months (minimum 3 months). The likelihood of reaching a uPSA of ≤ 0.01 ng/ml at 3 months is 73% for the first 100 patients. This is statistically lower when compared with 83% ($P < 0.05$) for the second 100 patients and 80% for the third 100 patients ($P < 0.05$). Overall, 84% of patients with pT2 disease and 66% patients with pT3 disease had a uPSA of ≤ 0.01 ng/ml at 3 months. Pre-operative PSA, PSA density and Gleason score were not correlated with outcome as determined by a uPSA of ≤ 0.01 ng/ml at 3 months. Positive margins correlate with outcome as determined by a uPSA of ≤ 0.01 ng/ml at 3 months but operative time and tumour volume do not ($P < 0.05$). Attempt at nerve sparing had no adverse effect on achieving a uPSA of ≤ 0.01 ng/ml at 3 months.

CONCLUSIONS uPSA can be used as an early end-point in the analysis of oncological outcomes after radical prostatectomy. It is one of many measures that can be used in calculating a surgeon's learning curve for laparoscopic radical prostatectomy and in bench-marking performance. With experience, a surgeon can achieve in excess of an 80% chance of obtaining a uPSA nadir of ≤ 0.01 ng/ml at 3 months after laparoscopic RRP for a British population. This is equivalent to most published open series.

KEYWORDS

Laparoscopic radical prostatectomy – Ultrasensitive prostate specific antigen assay – Learning curve

CORRESPONDENCE TO

Richard Viney, Department of Urology, Queen Elizabeth Hospital, Birmingham B15 2TH, UK

E: richviney@hotmail.com

Prostate cancer is now the commonest cancer in men in the UK and North America. Approximately 27000 new cases in England were reported in 2003 with 8500 deaths (United Kingdom Association of Cancer Registries [UKACR] <www.ukacr.org>). In the UK, 66.1% of patients have organ confined prostate cancer at presentation, a further 20.9% have locally advanced prostate cancer and the remaining 13% have metastatic disease at presentation (The British Association of Urological Surgeons [BAUS] <www.baus.org.uk>).

Radical treatment options are indicated in patients with organ confined prostate cancer. In suitably selected patients, radical retropubic prostatectomy is the treatment of choice.[1] Traditionally, this operation was performed via an open lower abdominal incision but the laparoscopic approach is becoming increasingly popular with oncological equivalence, improved morbidity and a quicker recovery.[2,3]

Laparoscopic radical prostatectomy (LRP) is a complicated and technically demanding operation with a flat (*i.e.*

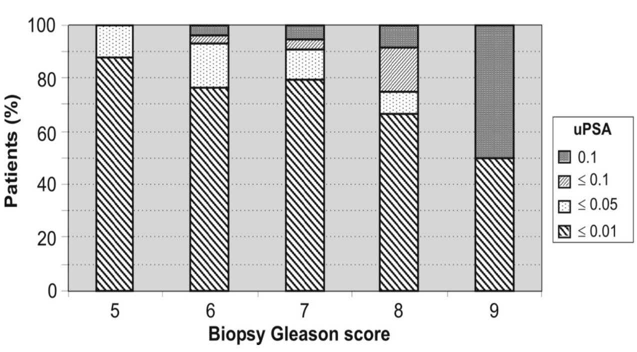
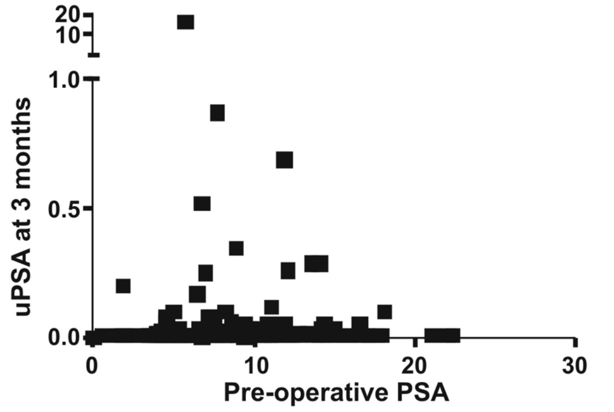


Figure 1 Biopsy Gleason score and uPSA at 3 months after surgery.



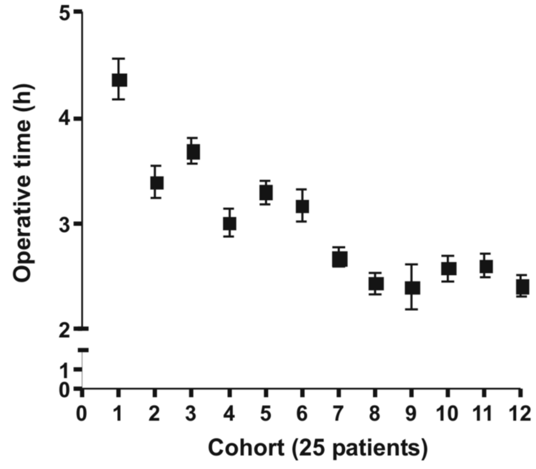
Pearson *r*	-0.02625
95% confidence interval	-0.1540 to 0.1024
P-value (two-tailed)	0.6896
P-value summary	ns
Is the correlation significant? (α = 0.05)	No
r^2	0.0006890

Figure 2 Pre-operative PSA and uPSA at 3 months.

difficult) learning curve.[4] The concept of a learning curve was first introduced by the 19th century German psychologist Hermann Ebbinghaus. He identified that increasing the amount of material to be learned increases the time it takes to learn it in a logarithmic way. In 1936, the learning curve was first quantified in the aeronautical literature. It was noted that every time total aircraft production doubled at Wright-Patterson Air Force Base in the US, the required labour time decreased by 10–15%.[5] Learning curves are measured by the length of time of the operation by most authors,[6,7] but it can be easily extended to other parameters such as surgical outcome measures or complication rate.

In both the laparoscopic and open setting, standard postoperative oncological surveillance is undertaken with serial prostate specific antigen (PSA) assessments to help identify patients in need of further treatment. Immediate treatment of patients who have local recurrence after radical prostatectomy with radiotherapy confers a survival advantage.[8]

We describe the use of ultrasensitive PSA (uPSA) determination in the oncological surveillance of patients undergoing LRP and its use as an oncologically relevant surrogate marker for monitoring the learning curve. In addition, we report on the surgical outcome of a single surgeon's first 300 patients.



	1	2	3	4	5	6	7	8	9	10	11	12
Mean	4.372	3.395	3.683	3.009	3.300	3.169	2.674	2.438	2.394	2.578	2.603	2.406
SD	0.9476	0.7185	0.5805	0.6369	0.5620	0.7301	0.4206	0.4031	0.8489	0.4977	0.4926	0.4171
SEM	0.1895	0.1607	0.1210	0.1358	0.1124	0.1490	0.09178	0.1008	0.2122	0.1244	0.1195	0.1043
Lower 95% CI of mean	3.981	3.059	3.432	2.727	3.068	2.860	2.482	2.223	1.941	2.313	2.350	2.184
Upper 95% CI of mean	4.763	3.731	3.934	3.291	3.532	3.477	2.865	2.652	2.846	2.843	2.856	2.628

Figure 3 Changes in operative time in consecutive cohorts of patients.

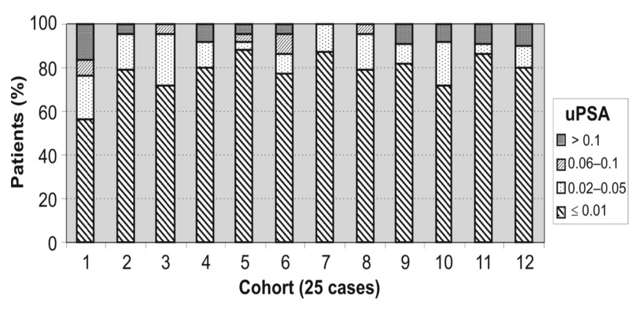


Figure 4 Distribution of uPSA at 3 months after surgery in sequential cohorts.

Patients and Methods

Between June 2003 and June 2006, 300 consecutive patients underwent laparoscopic extraperitoneal radical prostatectomy performed by a single surgeon. The technique used was a modified version of that described by Stolzenburg *et al.*[9] During the period of data collection, the technique underwent a number of modifications to improve potency and continence rates. These related to sparing the pelvic nerves and optimising the anastomosis by varying the number and type of anastomotic sutures. The patients' mean age was 62 years (range, 46–76 years) with a mean pre-operative PSA level of 7.37 ng/ml (range, 0.6–22.3 ng/ml) The median follow-up was 19 months (range, 3–39 months). The ultrasensitive assay used was Immulite 2000 Third Generation PSA. An undetectable uPSA was defined as ≤ 0.01 ng/ml. No patients were treated with hormones or radiotherapy within 3 months of surgery. Patients were followed on a 3-monthly basis initially. Statistical analysis was undertaken with Prism Graphpad v.4.00 statistical package.

Results

Patients with a Gleason score of ≥ 8 (n = 15) had a lower likelihood of achieving an undetectable uPSA compared with those patients with a pre-operative Gleason score of ≤ 6 (n = 145) although this was not statistically significant (P = 0.2586; Fig. 1). Similarly, there was no statistically significant correlation between pre-operative PSA (Fig. 2) or PSA density and uPSA at 3 months (r^2 0.00069 and 0.00011, respectively).

A steady reduction in operating time was noted from a mean of 262 min for the first 25 cases compared with 144 min for of the last 25 ($P < 0.01$; Fig. 3). Patients with operative times greater than 240 min were statistically less likely($P < 0.01$) to achieve an undetectable uPSA (66.6%) compared with operative times less than 120 min (90%). Non-nerve-sparing operations had significantly less chance of achieving an uPSA ≤ 0.01 ng/ml compared with unilateral or bilateral nerve sparing. Complications encountered in the series were five blood transfusions, four operations converted to open (these occurred in the first 20 cases but there were no other conversions in the subsequent 280 cases). There were four rectal injuries, two patients developed atrial fibrillation, there were two prolonged urinary leaks, one pulmonary embolus and one patient's catheter fell out at 2 days' post-surgery. The occurrence of complications was not associated with a significantly different uPSA result at 3 months. Alterations to operative technique did not correlate to uPSA at 3 months (r^2 0.0053).

Figure 4 shows the distribution of the uPSA levels at 3 months after surgery in sequential groups of 25 patients. The percentage of patients reaching an undetectable PSA at 3 months in the first 100 patients was 73% compared with 83% in the second 100 patients ($P < 0.05$) and 80% in the third 100 patients ($P < 0.05$). The case mix (stage, grade and tumour volume) was similar between these 25-patient cohorts.

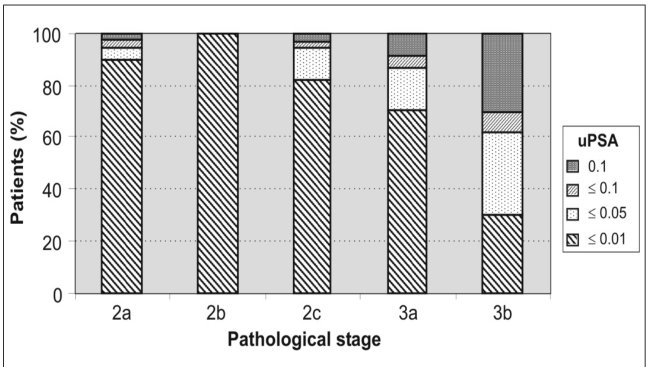


Figure 5 Pathological stage and uPSA at 3 months after surgery.

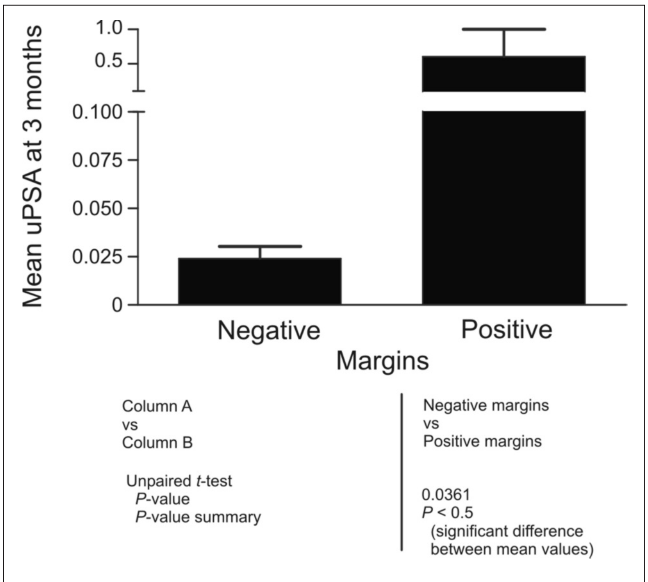


Figure 6 Impact of margins on uPSA at 3 months after surgery.

Overall, 39 patients (13.5%) were pT2a, four (1.3%) pT2b, 155 (53.6%) pT2c, 77 (26.6%) pT3a and 14 (4.8%) pT3b. Figure 5 demonstrates the uPSA reached at 3 months after surgery by pathological stage. Overall, 84% of patients with pT2 disease had an undetectable PSA compared with 66% of patients with pT3 disease. A negative surgical margin had an 88% likelihood of achieving a PSA nadir of ≤ 0.01 ng/ml. This was significantly more likely than if the margin was positive ($P = 0.0361$; Fig. 6). There was a positive correlation between tumour volume and uPSA at 3 months ($r^2 = 0.05312$). A tumour volume of less than 1 ml had an uPSA ≤ 0.01 ng/ml in 84% compared with only 61% if tumour volume was > 4 ml.

Discussion

uPSA assays are increasingly being used in post RRP surveillance. It has advantages over standard assays which are only sensitive to 0.1 μg/l in postoperative surveillance and prognostication. It allows for earlier detection of biochemical relapse by around 11–18 months over traditional methods.[11,16] Defining biochemical relapse in uPSA-monitored patients is still debated. Some authors feel there is too much 'background noise' at the very lowest levels to make this technique specific enough.[17] Others recommend that two sequential rises in uPSA is not specific enough and that one should wait to see four sequential rises before diagnosing biochemical failure.[16] By identifying and characterizing relapsing patients early, they can be offered salvage therapeutic interventions. It has been suggested that early salvage treatment helps increase the chance of relapse-free survival.[17]

In open RRP, patients whose nadir is ≤ 0.01 ng/ml have a 3% risk of biochemical relapse versus a 75% risk for those patients whose nadir is above this value.[15] Subsequent work has further stratified risk looking at various uPSA cut-offs in open RRP. These have consistently demonstrated relapse rates of 0–6% for those patients with a nadir of less than 0.01 ng/ml, relapse rates of 12–25% for a nadir of 0.01–0.04 ng/ml and relapse rates of 69–92% for a nadir of over 0.04 ng/ml.[13–15] The variation in these numbers is likely to be due, in part, to the variable length in follow-up.

This is the first report of the use of uPSA in a sequential series of patients undergoing laparoscopic RRP. As with patients having open surgery, the use uPSA in patients having laparoscopic procedures confers the advantages of detecting early biochemical failure, but also of providing a reproducible early end-point, particularly regarding oncological outcome. This paper demonstrates the use of this end-point in assessing the learning curve of laparoscopic radical prostatectomy.

Published series for open RRP have uPSA nadirs < 0.01 ng/ml, ranging from 52%[13] to 78%.[14,15] Using these data as a bench-mark against which we can assess the laparoscopic technique, our data compare favourably and support claims of oncological equivalence. The influence of intent to nerve spare is difficult to establish from these papers and may play a part as will the definitive disease stage but there is no correlation between intent to nerve spare and uPSA nadir in our data.

Given the uncertainty of the outcomes from this operation, in developing this series, the earlier patients were carefully selected creating a selection bias. As the technique improved, all suitable patients were offered either the laparoscopic or open technique. We note that this is not reflected in disease stage on pathology and disease burden by volume through the series. As the series has matured there has been inclusion of more challenging patients and these could bias the results in an adverse way.

In pT2 disease, 84% of patients had a uPSA nadir at 3 months of ≤ 0.01 ng/ml over the entire cohort. Appropriately staged patients undergoing laparoscopic RRP can enjoy oncological outcomes comparable to open RRP. Looking at pT3 disease, 66% of these patients also reach a uPSA of ≤ 0.01 ng/ml at 3 months. If one compares pT3a and pT3b, there is a large difference with 70% of pT3a versus 33% of pT3b having an uPSA level of ≤ 0.01 ng/ml at 3 months.

Looking at pre-operative parameters to try and stratify risk for patients, we find that there are trends towards poorer outcome with increasing biopsy Gleason score, pre-operative PSA and PSA density but there is no significant correlation.

Looking at peri-operative parameters to try and stratify risk for patients, we find that operative time and complications do not correlate with uPSA at 3 months although operations taking longer than 4 h do carry a significantly reduced likelihood of reaching a uPSA of 0.01 ng/ml or less at 3 months ($P < 0.001$). We also found that negative margins predisposed to a significantly improved uPSA at 3 months. There is a trend towards a greater chance of getting a uPSA of 0.01 ng/ml or less with decreasing tumour volume but this correlation is not significant.

These data suggest that bilateral or right-sided nerve sparing has a significant influence on outcome if judged by uPSA at 3 months when compared to no nerve sparing. This difference is not quite seen in the left-sided nerve preservation and this reflects the intra-operative observation that right-sided nerve preservation is technically easier for the right-handed surgeon. There is likely to be a strong selection bias. Patients with favourable pre-operative clinical staging and grading were likely to be offered a nerve-sparing procedure. This is likely to result in a more favourable outcome. Early cases were largely undertaken on patients unsuitable for non-nerve-sparing surgery due to the increasing complexity of offering nerve sparing as well as the ethical concerns when functional outcomes were still uncertain. This would also contribute to worse outcomes in this group.

In reviewing the literature, operative time is the commonest operative variable used to define learning curves. If the functional and oncological outcomes of radical prostatectomy were always the same, this would be the most valid variable to use. Operating time has the advantage of being easy to collect, immediate and is reproducible. As outcomes in surgery are variable, operative time may be of less value in measuring learning curves than other variables such as uPSA nadir. In Figure 3, mean operative time decreases as the series develops and plateaus around the 200th patient. This may seem like a long time but could be accounted for by the fact that the surgical technique was continuously evolving and, therefore, not stable. In Figure 4, patients achieving uPSA nadirs of < 0.01 ng/ml increase as the series develops and plateaus earlier, at around 100 patients. In the tenth cohort (patients 250–275), we note a drop in the number of patients achieving a nadir of < 0.01 ng/ml. This can be explained by the higher risk case mix in that particular cohort. When considering oncological outcomes by using uPSA nadir as a surrogate for oncological outcome (of < 0.4 ng/ml), the literature indicates that 250 open prostatectomies need to be performed by a single surgeon before the learning curve is complete.[18] Our data for the laparoscopic technique compare very favourably.

Conclusions

uPSA assessment in the postoperative surveillance of patients undergoing laparoscopic radical retroperitoneal prostatectomy for cancer has utility as a means of risk stratifying and counselling patients on prognosis. Our results demonstrate equivalence with published open data which gives us confidence in advocating this technique. We have demonstrated that nerve sparing does not appear to effect early outcome adversely as measured by uPSA. uPSA is an oncologically relevant early measure that can be used to assess a surgeon's learning curve.

References

1. Eastham JA, Scardino PT. Radical prostatectomy. In: Walsh PC, Retik AB, Vaughan EDJ, Wein AJ. (eds). *Campbell's Urology*, 7th edn. Philadelphia, PA: WB Saunders, 1998; 2547–64.
2. Tooher R, Swindle P, Woo H, Miller J, Maddern G. Laparoscopic radical prostatectomy for localized prostate cancer: a systematic review of comparative studies. *J Urol* 2006; **175**: 2011–7.
3. Hasan WA, Gill IS. Laparoscopic radical prostatectomy: current status. *BJU Int* 2004; **94**: 7–11.
4. Vickers AJ, Bianco FJ, Serio AM, Eastham JA, Schrag D, Klein EA *et al*. The surgical learning curve for prostate cancer control after radical prostatectomy. *J Natl Cancer Inst* 2007; **99**: 1171–7.
5. Wright TP. Factors affecting the cost of airplanes. *J Aeronaut Sci* 1936; **3**: 122–8.
6. Rassweiler J, Sentker L, Seemann O, Hatzinger M, Rumpelt HJ. Laparoscopic radical prostatectomy with the Heilbronn technique: an analysis of the first 180 cases. *J Urol* 2001; **166**: 2101–8.
7. Raman JD, Dong S, Levinson A, Samadi D, Scherr DS. Robotic radical prostatectomy: operative technique, outcomes, and learning curve. *J Soc Laparoendosc Surg* 2007; **11**: 1–7.
8. Bolla M, van Poppel H, Collette L, van Cangh P, Vekemans K, Da Pozzo L *et al*.; European Organization for Research and Treatment of Cancer. Postoperative radiotherapy after radical prostatectomy: a randomised controlled trial (EORTC trial 22911). *Lancet* 2005; **366**: 572–8.
9. Stolzenburg JU, Rabenalt R, Do M, Ho K, Dorschner W, Waldkirch E *et al*. Endoscopic extraperitoneal radical prostatectomy: oncological and functional results after 700 procedures. *J Urol* 2005; **174**: 1271–5.
10. Doherty AP, Bower M, Smith GL, Miano R, Mannion EM, Mitchell H *et al*. Undetectable ultrasensitive PSA after radical prostatectomy for prostate cancer predicts relapse-free survival. *Br J Cancer* 2000; **83**: 1432–6.
11. Vassilikos EJ, Yu H, Trachtenberg J, Nam RK, Narod SA, Bromberg IL *et al*. Relapse and cure rates of prostate cancer patients after radical prostatectomy and 5 years of follow-up. *Clin Biochem* 2000; **33**: 115–23.
12. Terai A, Matsui Y, Yoshimura K, Arai Y, Dodo Y. Salvage radiotherapy for biochemical recurrence after radical prostatectomy. *BJU Int* 2005; **96**: 1009–13.
13. Nakamura M, Hasumi H, Miyoshi Y, Sugiura S, Fujinami K, Yao M *et al*. Usefulness of ultrasensitive prostate-specific antigen assay for early detection of biochemical failure after radical prostatectomy. *Int J Urol* 2005; **12**: 1050–4.
14. Shen S, Lepor H, Yaffee R, Taneja SS. Ultrasensitive serum prostate specific antigen nadir accurately predicts the risk of early relapse after radical prostatectomy. *J Urol* 2005; **173**: 777–80.
15. Sakai I, Harada K, Kurahashi T, Muramaki M, Yamanaka K, Hara I *et al*. Usefulness of the nadir value of serum prostate-specific antigen measured by an ultrasensitive assay as a predictor of biochemical recurrence after radical prostatectomy for clinically localized prostate cancer. *Urol Int* 2006; **76**: 227–31.
16. Shimizu F, Tanaka S, Matsuyama Y, Tominaga T, Ohashi Y, Fujime M. Efficiency of ultrasensitive prostate-specific antigen assay in diagnosing biochemical failure after radical prostatectomy. *Jpn J Clin Oncol* 2007; **37**: 446–51.
17. Taylor 3rd JA, Koff SG, Dauser DA, McLeod DG. The relationship of ultrasensitive measurements of prostate-specific antigen levels to prostate cancer recurrence after radical prostatectomy. *BJU Int* 2006; **98**: 540–3.
18. Vickers AJ, Bianco FJ, Serio AM, Eastham JA, Schrag D, Klein EA *et al*. The surgical learning curve for prostate cancer control after radical prostatectomy. *J Natl Cancer Inst* 2007; **99**: 1171–7.